Physical Activity across the Cancer Continuum: Report of a Workshop

Review of Existing Knowledge and Innovative Designs for Future Research†

The Scientific Program Committee

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Research on the association between physical activity and cancer incidence has evolved rapidly over the last decade. Considerable data indicate a 40–50% reduction in colon carcinoma incidence in active compared with sedentary individuals and a 30–40% reduction in breast carcinoma incidence among women engaging in three or more hours per week of regular vigorous activity. Somewhat more limited and less consistent data associate prostate and lung carcinoma with inactivity.[1,2] Since the 1940s, body weight, body fat distribution, and adult weight gain have been linked to the development of endometrial, postmenopausal breast, colon, esophageal, and renal carcinoma incidence and breast carcinoma prognosis.[3,4] These studies also point to a possible role for physical activity on cancer incidence because of the interrelationship between weight and physical activity.

Biologic mechanisms that might explain the complex relationship between energy balance, weight, physical activity, and disease are diverse. They include sex hormones, insulin-related growth factors, cytokines, prostaglandins (PGs), and measures of immune function and free radical damage.[2]

Advances and dissemination of effective screening and treatment have increased the proportion and number of cancer patients diagnosed with early-stage cancer. These patients are likely to have excellent prognosis and live many years with cancer. Both newly diagnosed cancer patients and long-term cancer survivors are interested in learning about nontherapeutic agents that may improve both quality of life and longevity. Regular physical activity improves the quality of life and general feeling of well-being in relatively healthy populations.[5] Preliminary studies in cancer patients have demonstrated the beneficial effect of physical activity on quality of life during and after therapy and suggest a promising area for future research.

Given the growing evidence on the possible role of physical activity across the spectrum of cancer control, a meeting was organized to summarize current knowledge about physical activity and cancer and to suggest future directions for research. The meeting on Physical Activity and Cancer, held in Dallas on November 5–7, 2000, was the third meeting in the Cooper Institute Conference Series. Meetings in this series have the objectives of focusing on a specific research topic by leading international investigators to stimulate future research, set directions, and provide a forum to attract new investigators to the field. The 2000 meeting was sponsored by the American Cancer Society, the National Cancer Institute, the Centers

TABLE 1
Overview of Topics Presented at Meeting on Physical Activity and Cancer

Review of epidemiology	Review of possible mechanisms	Measurement of physical activity and fitness	Mechanisms for physical activity and cancer	Other issues
Epidemiology of physical activity and cancer	New theories of genetic and environmental interaction in cancer etiology and prognosis Cancer etiology: are we looking in all the right places?	Relevant time periods and parameters of exposure for risk reduction Feasibility and methods of incorporating fitness measures in large epidemiologic studies Cognitive aspects of survey questions for physical activity Validation and reliability issues of physical activity assessment	Reproductive hormones Physical activity, prostaglandin, E_2, and colon cancer Energy balance Insulin/IGF-1 Free radicals, genetic damage, and some sequelae Immune function and cancer Physical activity, stress, and cancer	Effects of confounding and effect modification: weight, nutrition, socioeconomic status, stress, obesity Physical activity as a catalyst for other lifestyle changes: physical activity interventions in smokers Physical activity interventions with cancer patients Effects of physical activity on cancer prognosis Lessons learned from previous research on other health issues

for Disease Control and Prevention, the Cooper Institute, and was held in cooperation with the American College of Sports Medicine.

The program for this conference focused on the epidemiology of physical activity and cancer, new theories of genetic and environmental interaction in cancer etiology and prognosis, methodologic issues in the assessment of exposures, possible biologic mechanisms for physical activity and cancer associations, issues of confounding and effect modification, interrelationships of physical activity and cancer-related health behaviors, and clinical studies of physical activity in cancer patients. Tables 1 and 2 provide a summary of the program outline, speakers, planning committee, and session moderators.. The following sections include a summary of the presentations and recommendations for future research.

Review of Epidemiology (Presented by Dr. I-Min Lee)

Epidemiologic investigations of the relationship between physical activity and cancer are of relatively recent origin. This is in contrast to a much more lengthy and substantial literature on cardiovascular disease (CVD) that conclusively documents the deleterious impact of a sedentary lifestyle.[5] The evidence that physical inactivity might be associated with increased risk of cancer is relatively strong for colon carcinoma and suggestive for breast and prostate carcinomas.[2,5,6] Data on colon carcinoma are collected from about 50 cohort and case–control studies of occupational and leisure time physical activity that show a rather consistent inverse association between incidence or mortality and physical activity. These studies display an average reduction in risk of colon carcinoma of 40–50%% among active individuals. This is encouraging because the level of activity associated with this reduction is not that obtained by highly trained athletes and is readily achievable by a large segment of the population.

Results from epidemiologic studies of carcinomas of the breast and prostate are less consistent than those for colon carcinoma. More than 40 studies of breast carcinoma have been conducted and have shown an average reduction in risk of approximately 30%, whereas approximately 30 studies of prostate carcinoma report an average reduction of 20%. These associations, although not large, nevertheless offer optimism for substantial preventive actions against these leading cancers in women and men. The information on other cancer sites is too limited and inconsistent to draw solid conclusions, except for rectal carcinoma for which the data are reasonably convincing that there is no effect. The data indicate that physical inactivity may be associated with important cancers with quite different etiologies. This underscores the need for carefully designed investigations to evaluate cancers already linked to physical activity and to initiate and expand research on other sites.

Review of Mechanisms of Cancer Etiology (Presented by Drs. Carl Barrett and John Potter)

Mechanisms by which physical activity might affect cancer risk are largely speculative.Because physical activity has affects on multiple biologic systems, many mechanistic pathways are possible. Profitable approaches to explore possible mechanisms of action are to consider well characterized etiologic pathways for cancer, as well as exciting new findings from experimental research. The well established phenomenon of a reduction in cancer rates among laboratory animals and humans on restrictive caloric diets provides clues to potential mechanisms relevant to phys-

TABLE 2
Speakers, Presentations, and Moderators and Facilitators[a]

Speakers	Junior investigator award presentations	Moderators and facilitators	Scientific program committee
Carl Barrett	Lisa Colbert	Louise Brinton	Rachel Ballard-Barbash
Steven Blair	Charles Matthews	Timothy Church	Aaron Blair
Christine Friedenreich	Tahereh Moradi	Martin Collis	Steven Blair
Frank Gilliland	Kathryn Schmitz	Colleen Doyle	Tim Byers
William Haskell		Robert Hoover	Laurie Hoffman-Goetz
Leena Hilakivi-Clarke		James Kampert	I-Min Lee
James Hill		Andrea Kriska	Richard Troiano
I-Min Lee		Carol Macera	Kim Westerlind
Bess Marcus		Julia Rowland	
Maria Elena Martinez		Charles Sterling	
Anne McTiernan		Sheila Zahm	
Hinnak Northoff			
Michael Pollak			
John Potter			
Anna Schwartz			
Marty Slattery			
Barbara Sternfeld			
Jeffrey Woods			
Gordon Willis			

[a] Four poster presentations were submitted by foreign participants. Two junior investigator presentations were submitted by foreign countries, as well as two with a author from the United States with other authors from a foreign country. There were 15 foreign registrants.

ical activity.[7,8] Dietary restriction appears to lower insulin-like growth factor I (IGF-I) in humans and rats. The restoration of IGF-I levels in calorie-restricted animals to levels occurring in animals on nonrestrictive diets increases cancer development.[9] Caloric restriction may slow the development of cancer by favoring apoptosis over cell proliferation. As one of the major components of energy balance, effects of physical activity on cancer development may operate through this pathway (Dr. Barrett).

Cancer etiology studies might be more informative if they focus on plausible protective factors, such as physical activity, as well as on risk factors that increase the initiation and progression of cancer (Dr. Potter). Focusing on factors involved in both prevention and promotion at the cellular and macro level is likely to provide the most effective strategy in characterizing cancer etiology. Evaluating a combination of preventive factors that influence etiologic pathways at a number of points may help explain a larger fraction of the variance in cancer risk than the more common individual factor approach. This approach would necessitate very large studies.

A more precise characterization of tumors might help to identifycancer risk factors (Dr. Potter). For example, microsatellite instability (MSI) has been effective in refining the subtypes of colon carcinoma. MSI occurs in approximately 15% of colon tumors and is reportedly more common among older individuals, women, and smokers, who may have a different constellation of risk factors than others with colon carcinoma.[10] It is unclear whether physical activity contributes specifically to MSI colon carcinoma, but this should be evaluated.

Review of Possible Mechanisms for the Association of Physical Activity and Cancer (Presented by Drs. Anne Mctiernan, Kim Westerlind, James Hill, Michael Pollak, Ninnak Northoff, Jeffery Woods, and Leena Hilakivi-Clarke)

Multiple mechanisms to explain the association between physical activity and cancer risk have been postulated and may vary depending on the characteristics of the individual (e.g., age, gender, health, fitness status, type of cancer) and stage of the carcinogenic process (e.g., preneoplasia, initiation, promotion, progression, and metastasis). Certain mechanisms may be cancer specific, such as steroid hormone perturbations and reproductive cancers. Others, such as alterations in IGF-I levels and body weight maintenance, may effect several cancers.

Although it is believed widely that exercise-associated modulation of endogenous reproductive hormones has a mechanistic role in breast carcinoma risk, direct evidence on the impact of physical activity on endogenous hormones is relatively limited. The majority of studies that have examined the effects on reproductive hormones have been done in elite women athletes (Dr. McTiernan) and the minimal level of activity required to change endogenous hormones, such as estrogen or progesterone, is unclear. Another complication is that it is unclear if exercise alone effects hormone levels or if changes in body mass are also required. Intervention studies have been small, have had problems with subject adherence, and have demonstrated frequently altered hormone levels only in the weight loss groups. Data are even more limited on whether physical activity alters testosterone or sex hormone binding globulin in men and whether such changes have a role in the development of prostate or testicular carcinoma. There is a need to assess the effects of physical activity and reproductive hormone levels in relation to cancer and early endpoints such as mammographic densities for breast carcinoma and prostate specific antigen (PSA) for prostate carcinoma, to genetic polymorphisms, such as BRCA1, and to other hormones and growth factors (e.g., IGF-I). IGF-I is a powerful mitogen that increases cell proliferation and inhibits apoptosis and may be affected by physical activity. An increase in IGF-I and a decrease in its major binding protein (i.e., IGFBP-3) may be associated with many tumors (Dr. Pollak) as noted in the excellent review by Yu and Rohan.[11] Increased IGF-I bioactivity may increase cancer risk by allowing the survival of partially transformed clones of epithelial cells, providing the opportunity for further genomic damage and neoplastic transformation. Data from the few studies that have examined if physical activity affects IGF-I and/or IGFBP-3 levels are mixed. Additional studies should examine this potential mechanism of risk modification.

Several mechanisms have been proposed to explain the effect of physical activity on colon carcinoma risk, including changes in transit time, altered gut mucosal immunity, altered bile acid metabolism, and lower insulin and PG levels. It is well known that nonsteroidal antiinflammatory drug use inhibits colorectal mucosal PGE2 synthesis. Cross-sectional analyses of baseline data from the Piroxicam Trial (Dr. Martinez) indicate that self-reported physical activity was inversely correlated with levels of PGE2 in rectal mucosal biopsies and it could affect risk through reduced transit time or cell proliferation rates. However, the absence of an effect of physical activity on rectal carcinoma in epidemiologic research makes this finding difficult to interpret. There was also an inverse relation between PGE2 and body mass index (BMI) that underscores the need to disentangle possible fitness and weight effects.

A variety of energy balance-related issues should be considered in light of the cancer–physical activity relationship. These include the pattern of fat distribution (i.e., subcutaneous, visceral, android, gynoid), the contribution of metabolic products of adipocytes (i.e., lactate, leptin, angiotension, plasminogen activator inhibitor-1, free fatty acids), the steroid hormone production in and sensitivity of adipose tissue, and the effect of weight cycling at various critical time periods of adipocyte development. The issue of metabolic fitness, whereby an individual can increase physical activity and fitness without a concomitant change in weight, also needs to be addressed in the physical activity–energy balance–cancer relationship (Dr. Hill).

Exercise has been long believed to enhance immune surveillance and to increase resistance to cancer development. Extensive evidence indicates that exercise increases immune cell (i.e., T lymphocytes, natural killer cells, B cells, and macrophages) number and activities and that the effect on immune function is modified by the intensity of the exercise, but the link to human cancer is not clear (Dr. Woods). An inverted J response (i.e., moderate levels of exercise enhance immune function whereas high and low levels appear to have negative effects) has been observed repeatedly. Immune function–exercise–cancer research is needed in humans involving peripheral blood cell counts, antibody levels, cytokine levels, and function assays and in animals in which mechanisms can be tested experimentally and the effects of transplanted, viral, spontaneous, and chemically induced tumors can be evaluated.

Inhibition of cancer development via exercise may be mediated through its effect on reactive oxygen species and DNA damage (Dr. Northoff). Free radicals have many functions, including signal transduction, proliferation and activation of certain cells and cytokines, and DNA damage. Both DNA damage and repair occur continuously and there exists the potential for misrepair leading to DNA restructuring, mutagenesis, and carcinogenesis and physical activity may affect this balance. Acute exercise appears to result in an increase in free radicals, increased consumption of endogenous tissue antioxidants, an increase in lymphocyte apoptosis, and DNA damage that peaks 24–48 hours after exercise. In contrast, trained individuals appear to have a consistent decrease in the amount of DNA damage at rest compared with their untrained counterparts. Whether the alterations in free radical formation and DNA damage are linked to cancer is not clear.

Exercise may affect cancer development through its role as a stressor or stress reducer (Dr. Hilakivi-Clarke). Animal data indicate that certain stressors (i.e., foot shock and isolation) increase tumor incidence, whereas others (i.e., handling, restraint) decrease cancer outcomes. Although there is a popular belief that increased levels of stress are associated with increased cancer occurrence in humans, the evidence is very limited. The balance between stressor and stress reducer roles and/or on timing of the stress (exercise) exposure may be critical, but information on these pathways in cancer development is scant.

Despite a growing interest in the epidemiology of physical activity and cancer, the biologic mechanisms that might underlie these associations have been investigated poorly and sporadically. Carcinogenesis is a lengthy and complex process and although the potential impact of physical activity across the life span is great, the mechanisms and types of exercise may vary depending on subject and disease characteristics. Development of a better understanding of how exercise influences carcinogenesis is critical. This will require collaboration between scientists from multiple disciplines and integration of methodologic approaches to evaluate critically how physical activity mediates the biology of cancer risk reduction.

Measurement of Physical Activity and Fitness (Presented by Drs. Christine Friedenreich, Steven Blair, Gordon Willis, and Barbara Sternfeld)

Measurement of habitual physical activity is difficult. Although sophisticated instruments have been developed to assess physical activity, those employed in cancer research are often simplistic and the measurements are often crude and imprecise. In many studies, physical activity measures have been cursory, sometimes as brief as a single question. It is doubtful that such a simple approach can capture much of the variability in physical activity in a population. The current literature on physical activity as a factor in cancer risk is therefore difficult to interpret (Dr. Friedenreich). Such an approach would certainly not be acceptable in other areas of cancer research such as diet, reproductive factors, or tobacco and alcohol use. It is not sufficient for physical activity either. The effect of physical activity on cancer risk may well have been underestimated because of substantial misclassification that results from use of these simplistic scales (Dr. Blair). When investigators have attempted to measure physical activity in more than a cursory way, comparison between studies is often impossible because of the use of widely differing measurements.

Application of better measures of physical activity for the study of cancer is needed. Some have been developed for cardiovascular epidemiology (Dr. Blair). Comprehensive assessments of physical activity should include measures of frequency, duration, and intensity. All types of physical activity should be ascertained, including recreational, occupational, and household activities (Dr. Sternfeld). Because there may be a long latency between cancer and its etiologic factors, lifetime retrospective histories of physical activity should be developed and validated for use in epidemiologic studies.

Questionnaire design can be very complex and cognitive interpretation of questions can often be quite different from what was intended by the investigator (Dr. Willis). Problems of assessment include term vagueness and uncertain frames of reference. It is best to avoid questions that require the respondent to report on behaviors during a "usual day" because there can be widely varying interpretations of this phrase. Questions are often cognitively complex when they mix frequency, duration, and intensity into a single question. This means that simple, global questions cannot be expected to be very accurate as to the "dose" of physical activity. However, simple global questions can be a useful screen for very high or very low or sedentary levels of activity. When collecting information on lifetime history of behaviors, it is usually a simpler cognitive task to ask respondents to recall that information backwards in time, beginning with the present.

Future studies of cancer should consider measuring cardiorespiratory fitness, not just physical activity (Dr. Blair). Although the relative, independent contributions of physical activity and fitness to cancer are not known, cardiorespiratory fitness may predict CVD and all-cause mortality better than do measures of activity alone. It might do the same for cancer. For example, Olivera et al. report a significant trend for fatal and nonfatal prostate carcinoma across quartiles of cardiorespiratory fitness ($P < 0.004$), but no trend was observed across quartiles of physical activity ($P = 0.83$).[12] There are a number of techniques to assess fitness that are feasible for field studies, including submaximal exercise testing on a treadmill, which is now included in the National Health and Examination Survey (NHANES) IV.[4]

Intervention trials of physical activity and intermediate markers of cancer risk would be helpful to assess mechanisms of action and to validate and standardize assessment procedures. Short-term validation studies show correlation coefficients of about 0.4–0.6 between doubly-labeled water estimates of activity, the current "gold standard" of energy expenditure, and activity as measured by both questionnaires and accelerometers (Dr. Sternfeld). Validity is generally better for self-reports of vigorous activity than for measures of moderate activity.

The impact of physical activity on cancer risk may be underestimated substantially. Physical activity estimates used in epidemiologic studies are much less precise than are measures of factors with which activity is related, including diet and BMI, because only a few questions typically are devoted to assessing activity. Physical activity can be assessed with the same precision as diet, an equally complex behavior — currently most often assessed by self-report, and an effort similar to that employed for other areas is needed if we are to accurately evaluate its impact. Finally, for some diseases, psychological responses to physical activity may be as important as the physical activity per se. Psychological effects are not measured with objective measures of activities and cannot be assumed readily to be uniform for all people. As Dr. Sternfield noted, “The chase is different for the fox than for the dog.”

Effects of Confounding and Effect Modification (Presented by Dr. Marty Slattery)

Confounding and effect modification are relevant to any area of epidemiologic investigation. Inconsistency among study results, such as seen in the relationship between physical activity and some cancers, heightens concern about these phenomena. Using a recent large case–control study of colon carcinoma as a model to examine the effects of confounding and effect modification, Dr. Slattery found that physical activity was associated with the disease outcome, as seen in many studies. There was little or no association, however, between physical activity and a number of potential confounders, such as body size, cigarette smoking, alcohol intake, aspirin or other nonsteroidal antiinflammatory drug use, family history of colon carcinoma, multivitamin use, or dietary factors. In addition, they do not appear to be confounders in the association between physical activity and colon carcinoma. Unlike confounding, which is problematic, and needs to be removed, effect modification can provide clues about biologic mechanisms and etiologic pathways. Effect modifiers may explain inconsistent results in populations with different distributions of these factors. In the above case–control study in which there was no confounding between physical activity and other colon carcinoma risk factors, considerable effect modification was found. Physical activity had a stronger effect on colon carcinoma risk among participants who were male, had a high BMI, a low vegetable intake, or a more “Western” rather than a “prudent” diet.[10] These findings suggest that etiologic pathways may differ for men and women, with estrogens and hormone replacement therapy playing a role for women, and that the effect of physical activity may be influenced by diet. Evaluation of effect modification is challenging. Large sample sizes and precise measures of association are needed.

Physical Activity as a Catalyst for Other Lifestyle Changes (Presented by Dr. Bess Marcus)

Physical activity may affect cancer by serving as a catalyst for changes in other lifestyle risk factors. Intervention programs that combined smoking cessation with weight control through dietary modification have not been successful at increasing cessation rates or minimizing weight gain. Smoking cessation by itself is a difficult behavioral change and to diet simultaneously is extremely difficult. Participation in physical activity may provide an alternative to dietary restriction as an adjunct to control weight gain commonly observed with smoking cessation. Physical activity not only increases energy expenditure, but also may help to reduce depressed affect, tension, and the fear of postcessation weight gain. Unfortunately, many studies that have considered physical activity have had small samples, a limited exercise program, an inadequate cessation program, or inadequate control for contact time.

Dr. Marcus described a recent study that compared the effects of supplementing a behavioral smoking cessation intervention for women with either participation in a regular vigorous exercise program or the same amount of contact time discussing women’s health issues. The exercise group had better quit rates, with one half as much recidivism as in the control group after 1 month. Early in the program, the exercise group gained 2.7 kg, whereas the control group gained 5.4 kg. This difference was eliminated by Week 20 because the exercise group stopped exercising after the program ended. VO_2 increased to the same extent among those who exercised, but did not quit smoking, as it did among those who quit smoking but did not exercise. The improvements in VO_2 due to quitting smoking and exercising were additive. Exercise was believed to improve cessation by reducing weight gain, decreasing dietary restraint, and minimizing the increase in sadness as measured on a depression scale. As is common in many reported exercise interventions, adherence may be difficult. In this study, there was substantial, albeit nondifferential, dropout after randomization in both the exercise and control groups. Although differential dropout in exercise versus control groups might alter validity of results, nondifferential dropout should not.

Physical Activity among Cancer Patients: Quality of Life and Prognosis (Presented by Drs. Anna Schwartz and Frank Gilliland)

Cancer patients not only want a cure, they also want a full and active life. Cancer treatment often decreases an individual's capacity to participate in routine activities and increases the risk for other diseases such as CVD, osteoporosis, obesity, and emotional problems. Recent exercise interventions for cancer patients have shown some intriguing benefits. Yet, it is rare for cancer patients to be encouraged to exercise, particularly during the active period of treatment.

Studies of exercise in cancer patients vary widely by cancer site, the type of cancer treatment being received, as well as by the intensity, frequency, and duration of exercise prescribed. In general, studies have been small, nonrandomized, limited in terms of ethnic representation, and most have been home-based studies with little control over the dose of physical activity received. Despite these caveats, physical activity may be feasible, may be well tolerated by cancer patients, and may have beneficial effects on functional ability, fatigue, side effects of therapy, psychological status, quality of life, and body composition (Dr. Schwartz).[13] Future research needs to assess whether this type of program is cost-effective and generalizable to other populations, to evaluate the benefits of moderate intensity physical activity, to provide better guidance on individualizing exercise prescriptions by diagnosis and treatment protocols, and to explore means to maintain physical activity levels after formal program termination.

To our knowledge, information concerning the effect of physical activity on cancer prognosis is virtually nonexistent. With increasing early detection and length of survival, interest has grown in identifying factors that decrease recurrence, improve quality of life, and increase longevity. Although to our knowledge there are few studies linking physical activity to breast carcinoma outcomes, the existing data and the relationship between postdiagnosis weight gain and poorer prognosis provide the rationale for further exploration.

Future studies of physical activity and breast carcinoma prognosis should consider mechanisms and causal paths (Dr. Gilliland). These are needed not only for causal inference, but also to tailor physical activity recommendations. We need to be able to prescribe the type and amount of exercise. In addition, we need to know the levels of energy flux and energy balance based on type of treatment, as well as the genetic characteristics of the patient and the tumor genotype and phenotype. Intermediate markers and biologic mediators are needed to predict patient outcome. Candidate markers are hormones, binding proteins, and insulin sensitivity. The Healthy Eating and Lifestyle study, a population-based prospective cohort study, is designed to examine the effects of physical activity, diet, and body weight on breast carcinoma outcomes (Dr. Gilliland). Outcomes include recurrence of breast carcinoma, mammographic density, survival and quality of life, and measures to address mechanistic questions, such as hormones and genetic tumor markers.

Future research on physical activity and cancer prognosis needs to target improved understanding of the mechanism of effects of physical activity, to explore genomic and proteonomic aspects, and to evaluate multifactorial interventions with intermediate markers. Markers should include growth factors, cytokines, steroid hormones, binding proteins, receptors, and postreceptor signaling factors. Observational studies of breast carcinoma prognosis need better assessment of physical activity and they need consider measurement error.

Lessons Learned from Research on Other Health Issues (Presented by Dr. William Haskell)

The approaches of evidence-based and evidence-informed health care were described and contrasted. Insurance companies and others are increasingly supporting evidence-based practice. This approach requires results from multiple large randomized controlled trials (RCTs) to provide evidence. Such trials are not likely to occur for examination of the effect of behavioral changes, such as physical activity or tobacco cessation, on cancer development or survival. In these situations, evidence-informed health care integrates information from all sources, including observational studies, mechanism studies, andRCTs. This type of approach may be more appropriate than the evidence-based approach for deciding when to promote physical activity for cancer prevention. It is encouraging that the relationships between low-density lipoprotein or high-density lipoprotein cholesterol and coronary heart disease and between systolic blood pressure and stroke demonstrate that repeated, well designed observational studies are consistent with RCTs.

When considering an outcome such as body weight, total energy expenditure is the relevant factor and absolute intensity is the important measure. However, relative intensity of exercise may be the important factor for biologic responses pertinent to reduction of disease risks. Examples of mechanisms known to respond to relative intensity are splanchnic blood flow, catecholamine release, and enzyme activity. The same absolute intensity activity, such as walking at a 3.5-mile/hour pace, can be light activity for a young fit person, but a vigorous activity for an old or unfit person. Assessment of relative intensity is a challenge because some type of fitness test is required to estimate exercise capacity. This is a major difference between data collection in experimental and observational settings. Measures such as ratings of perceived exertion can help to normalize data without fitness testing.

Lessons from studies on physical activity and diseases other than cancer underscore the challenges of very low activity and fitness in patient populations. Bed rest results in detrimental changes in multiple biologic functions. Patients may spend 23.5 hours per day lying, sitting, and standing. Glucose tolerance decreases and blood coagulation increases rapidly with the onset of bed rest. Effects of bed rest will interact with the effects of cancer and its treatment. Therefore, public health recommendations for healthy populations cannot be applied routinely to patients. Unfortunately, there is little evidence regarding the best approaches to physical activity among cancer patients. One possible approach would be to give brief intermittent activities within the patient's capacity (Dr. Haskell). These could be for periods as short as a minute or less in the early recovery phase. Lessening the decline in functional ability is an important outcome. Self-reported ability can also show positive effects of physical activity.

Perspectives on Examining Physical Activity across the Cancer Control Continuum

Advances in cancer screening and/or treatment have occurred for breast, colon, and prostate carcinomas, three of the four most common carcinomas in the United States. These advances have led to an increase in the proportion of people who are diagnosed early and who live many years with cancer. These changing factors have led to an expansion in examining the effect of modifiable lifestyle factors on prognosis and quality of life, in addition to incidence. The data on the preventive effect of physical activity relative to cancer is strongest for these three cancers. Therefore, future research should be designed to examine the effect of physical activity and related lifestyle factors across the cancer control continuum. This effort, however, will only be successful if information on physical activity is sought with the same intensity as that for other risk factors.

Advances in basic and molecular research have the potential to greatly advance our ability to more completely characterize an individual's genetic predisposition to disease and physiologic response to specific exposures. These advances, coupled with cellular and molecular characterization of tumors, will eventually improve the ability to individualize risk and to target preventive and life-enhancing interventions. Better understanding of the differential impact at different stages of cancer development from initiation, through promotion, progression, and metastasis also will help to refine recommendations for interventions throughout life.

There is sufficient evidence to indicate that a physically active lifestyle is beneficial to warrant enhanced research to better describe and quantify its role, particularly in combination with weight control and healthy eating habits. The growth in evidence has led the World Health Organization and the International Agency for Research on Cancer to develop a prevention handbook on weight control and physical activity.[14]

Directions for Future Research

Future research directions presented below are not comprehensive, but are intended to give a sense of the scope of research that is needed to further advance this field. The ultimate goal of this research is to provide evidence of methods for preventing cancer and improving health and quality of life for people living with cancer.

Measurement and Methods

Error in the estimation of physical activity is undoubtedly substantial. It is probably greater than that demonstrated for diet because, in most studies, fewer questions are devoted to the assessment of physical activity than for diet. This is likely to lead to considerable misclassification and underestimation of effect of physical activity on any of the outcomes examined. Research on physical activity assessment should employ sophisticated statistical methods and biologic validation that are now seen as central to advances in dietary assessment methods. The research priorities below address these critical needs.

- Develop comprehensive physical activity instruments for self-report of physical activity. These instruments should include type of activity and measures of frequency, duration, and intensity, be based on current concepts of memory and cognitive processes, and should include lifetime retrospective histories of physical activity. As with diet, there may be a need to develop special instruments for gender and ethnic subgroups.
- Validate self-report measures of physical activity against objective measures of cardiorespiratory fitness and of motion, such as accelerometers. Substudies with doubly labeled water should examine the relationship between self-reported measures of physical activity and energy expenditure. Ideally,

such studies might be combined with validation studies of self-report measures of diet.

- Utilize advanced statistical theory to examine issues of measurement error to determine the extent of bias in existing risk estimates of physical activity. Validation substudies in large epidemiologic studies can utilize this methodology to correct risk estimates for measurement error from self-report.

Observational Studies of Incidence, Prognosis, and Quality of Life

- Incorporate into epidemiologic studies of cancer the best standardized and validated self-report measures of physical activity that include measures of frequency, duration, and intensity. Include objective measures of fitness (such as treadmill times) and motion (such as accelerometers). In very large studies, this might be done in a subset.
- Develop study designs that examine multiple interrelated health behaviors, such as weight control and physical activity, and their role in both cancer incidence and prognosis.
- Design studies to allow full consideration of confounding and effect modification for key postulated underlying biologic mechanisms, genetic predisposition for disease, and tumor characteristics. These studies should be developed both in the areas of examining risk for incident as well as recurrent disease.
- Incorporate biomarkers of physiologic response to physical activity that are relevant to cancer.

Mechanisms

- Conduct basic research in animal, in vitro, and in vivo models to expand our understanding of possible mechanisms through which physical activity and fitness impact cancer development.
- Develop animal models and study designs to examine the interrelated effect of diet, weight control, and physical activity on intermediate markers, such as sex steroids, IGF-I, binding proteins, PGs, DNA damage, and cancer outcomes.
- Examine variation in intermediate markers, such as immune function, or DNA damage and repair, for acute compared with chronic exercise training.
- Design animal experiments to examine postulated key periods of risk across the life cycle and during specific phases of the carcinogenic process.
- Utilize well controlled and characterized physical interventions in humans (RCTs) that include various combinations of physical activity to examine the effect on biologic intermediate markers of various types, intensities, and durations of physical activity.
- Include measurement of body composition in such studies to examine the independent and combined effect on these biomarkers of both physical activity and changes in body composition in the absence of changes in weight.
- Explore the combined effect of physical activity, weight control, and beneficial changes in body composition on biologic markers identified as key for weight-related cancers, using RCTs. Potentially important biomarkers for weight-related cancers include sex steroids, IGFs, hormonal binding proteins, receptor status, mammographic density, and PSA.

Clinical Interventions in Cancer Patients

- Expand the examination of the effect of physical activity on quality of life across the continuum of recovery for major cancers.
- Design interventions, including RCTs, in cancer patients to examine whether activity prescriptions should be individualized to diagnosis and treatment.
- Evaluate the effectiveness of different less intensive behavioral approaches to maintaining physical activity after initial intensive interventions. Evaluate whether these different approaches are cost-effective and generalizable to different populations.
- In RCTs or other appropriate study designs, examine the efficacy and effectiveness of physical activity combined with healthy eating habits in controlling weight both among health individuals and patients with cancers for whom prognosis is related to weight at diagnosis. Identify components of physical activity that are critical to cancer inhibition (i.e., type of activity, intensity, frequency, or duration).

REFERENCES

1. Colditz GA, Cannuscio CC, Frazier AL. Physical activity and reduced risk of colon cancer: implication for prevention. *Cancer Causes Control.* 1997;8:649–667.
2. McTiernan A, Ulrich C, Slate S, Potter J. Physical activity and cancer etiology: Associations and mechanisms. *Cancer Causes Control.* 1998;9:487–509.
3. Ballard-Barbash R. Energy balance, anthropometrics, and cancer. In: Heber D, Blackburn G, Go VLW, editors. Nutritional oncology. San Diego: Academic Press, Inc., 1999:137–153.
4. National Center for Health Statistics, Center for Disease Control. Cardiovascular fitness. In: National Health and Nutrition Examination Survey. Survey questionnaires, examination components, and laboratory components. http://www.cdc.gov/nchs/data/meccomp.pdf, 39–43. Accessed July 15, 2002.

5. U.S. Department of Health and Human Services, Centers for Disease Control. Physical activity and health: a report on of the Surgeon General. Atlanta: Centers for Disease Control, 1996.
5. Lee I-M, Sesso HD, Chen J-J, Paffenbarger RS Jr. Does physical activity prevent the development of prostate cancer? *Epidemiol Rev.* 2001;23:132–137.
7. Barrett JC. Molecular and environmental causes of cancer. *Drug Metab Rev.* 2000;32:139–142.
8. Gerber M, Corpet D. Energy balance and cancers. *Eur J Cancer Prev.* 1999;8:77–89.
9. Dunn SE, Kari FW, French J, et al. Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice. *Cancer Res.* 1997;57:4667–4672.
10. Slattery ML, Curtin K, Anderson K, et al. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. *J Natl Cancer Inst.* 2000;92:1831–1836.
11. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst.* 2000:92:1472–1489.
12. Oliveria SA, Kohl HW 3rd, Trichopoulos D, Blair SN. The association between cardiorespiratory fitness and prostate cancer. *Med Sci Sports Exerc.* 1996;28:97–104.
13. Courneya KS, Friedenreich CM. Physical exercise and quality of life following cancer diagnosis: a literature review. *Ann Behav Med.* 1999:21:171–179.
14. IARC Working Group on the Evaluation of the Evaluation of the Cancer:Preventive Agents. Weight control and physical activity. In: Vainio H, Bianchini F, editors. IARC handbooks of cancer prevention. Volume 6. Lyon, France: IARC Press, 2002:1–315.